A PHASE I STUDY OF AUTOLOGOUS HUMAN INTERLEUKIN 2 (IL-2) GENE MODIFIED TUMOR CELLS IN PATIENTS WITH REFRACTORY METASTATIC OVARIAN CANCER

SCIENTIFIC ABSTRACT

This phase I study in patients with advanced ovarian cancer is undertaken with a view toward developing an effective means of treating disseminated cancers. The rationale for this trial is based on extensive pre clinical studies in rodent tumor models supplemented by *in vitro* explorations of the genetic modification of human ovarian cancer cells.

Rodent cancer cell lines genetically modified by a retroviral vector containing cytokine genes have been screened for therapeutic anti-tumor activity. Screening included models of melanoma, sarcoma, renal cancer, lung cancer, colon cancer, bladder cancer, breast cancer, and prostate cancer. In a murine adenocarcinoma models (OCa ovarian, 4T1 breast, and Lewis lung), IL-2 gene transduction led to loss of tumorgenicity of previously tumorgeneic doses. Active immunotherapy of tumor bearing animals with lethally irradiated, IL-2 gene transduced tumor cells, demonstrated inhibition of tumor growth. The genetically manipulated cells did not grow or cause significant toxicities at the site of administration in pre clinical studies.

Using a novel non-viral method of gene delivery (liposomes) and a plasmid (pMP6A/IL-2) based on adeno associated virus (AAV) retroviral vector *in vitro* culture conditions, human ovarian cancer cells are transducible. In clinical trial simulations, over 80% of primary cultures of ovarian cancer cells were transduced successfully resulting in a range of IL-2 secretion at levels that have demonstrated to be in the range required for biologic results in the rodent models. In these feasibility studies, liposomal transfection with the human IL-2 gene lead to IL-2 secretion of over 1 ng/10^6 cells/24hr in human ovarian cancer cells. Irradiation experiments defined a dose where patient derived ovarian cancer cells were rendered non-replicative. Fortunately, post-transfection IL-2 secretion was not diminished by irradiation.

The overall objective of the Phase I portion of these studies is to evaluate this modality with respect to the safety of clinical administration and induction of anti-tumor immune responses. Escalating doses of lethally irradiated, autologous ovarian cancer cells expanded in short-term culture and transfected with the human IL-2 gene will be tested to determine the highest safely tolerated cell dose in the dose range feasible from ovarian cancer cells harvested from malignant ascites or following tumor debulking surgery. The dose range tested has pre clinical anti-tumor efficacy in ovarian carcinoma. Three primary objectives of the Phase I portion of this study are:

1. To evaluate the safety of skin injections of cultured, lethally irradiated, autologous IL-2 gene transfected ovarian cancer cells secreting IL-2 at 1-100ng/106 cells/24 hrs.

2. To describe and quantitate the acute toxicities, if any, of active immunotherapy with irradiated IL-2 gene transfected ovarian cancer cells.

3. To assay both *in vitro* and *in vivo* the contribution of active immunotherapy with IL-2 gene transfected ovarian cancer cells to the induction of specific anti-tumor immune responses in women with advanced ovarian cancer.